REMARKS

Status Summary

Claims 1-96 are pending. Claims 1-73, 80, and 88 are withdrawn from consideration as directed to nonelected inventions. Claims 74-79, 81-87, and 89-96 have been examined. The specification is objected to for improper reference to trademarks. Claims 81-82, 84, 86, and 90 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for recitation of "RITUXAN®." Claims 81-82, 84, 86, and 90 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to enable practice of the invention based on perceived inavailability / nonreproducibility of the RITUXAN® antibody. Claims 81-82, 84, 86, and 90 are also rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling one to practice the invention commensurate in scope with the claims. Claims 74-79, 81-87, and 89-96 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Alas et al. (1998) *Blood* 92:601A in view of Levy et al. (1994) *J Clin Invest* 93:424-428 and U.S. Patent No. 6,183,744 (Goldenberg).

The specification and claims 75, 81-82, 84, 86, and 90 are amended as indicated above. Reconsideration in view of the amendments and following remarks is respectfully requested.

Objection to the Specification

The disclosure is objected to as informal based on incomplete reference to trademarked materials. Office Action, page 2, item 4. The disclosure has been amended as appropriate. Applicant notes that "rituximab" is a non-trademarked description of the RITUXAN® antibody, which has been adopted by the United States Adopted Names Council (*see* enclosed letter).

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 81-82, 84, 86, and 90 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for recitation of "RITUXAN®." The examiner suggests that reference to a trademark is indicative of a composition's source in the absence of a description of the composition itself. Office Action, page 3, item 4. This rejection is respectfully traversed.

Claims 81-82, 84, 86, and 90 are amended to recite "RITUXAN® (rituximab)," which refers to both the trademarked composition and its generic description. Support for the amendment can be found in the specification as originally filed, for example at page 25, lines

21-22. Applicant respectfully requests inclusion of the trademark on the basis that RITUXAN® (rituximab) refers to a particular anti-CD20 antibody. The amino acid sequence of RITUXAN® (rituximab) is disclosed in U.S. Patent No. 5,736,137, which issued on April 7, 1998. Cells expressing the RITUXAN® (rituximab) antibody are publicly available from the American Tissue Type Collection as deposit number 69119. In addition, the descriptive term "rituximab" has been adopted by the United States Adopted Names Council (*see* enclosed letter). The particularity of the term "RITUXAN® (rituximab)" is recognized in the art, including in journal publications and in the claims of issued U.S. patents. *See e.g.*, U.S. Patent Nos. 6,486,204, 6,462,041, and 6,462,017.

Based on the foregoing arguments, claims directed to the use of RITUXAN® (rituximab) are believed to be described with sufficient particularity as required by 35 U.S.C. § 112, second paragraph. Thus, withdrawal of the rejection of claims 81-82, 84, 86, and 90 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

First Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 81-82, 84, 86, and 90 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling practice of the invention because it is uncertain whether the RITUXAN® (rituximab) antibody is known and publicly available and/or reproducible from the written description. Office Action, page 4, item 8. This rejection is respectfully traversed.

As detailed herein above, the RITUXAN® (rituximab) antibody is well known in the art. Cells expressing the RITUXAN® (rituximab) antibody are publicly available as deposit number 69119 from the American Tissue Type Collection. Based thereon, this rejection of claims is believed to be rendered moot, and withdrawal of the rejection of claims 81-82, 84, 86, and 90 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Second Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 81-82, 84, 86, and 90 are also rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling one to practice the invention commensurate in scope with the claims. The examiner states that the specification is enabling for a method of treating B cell lymphoma in a patient by administration of the anti-CD20 antibody C2B8. However, it is contended that methods comprising administration of RITUXAN® are not enabled because it is unclear what components or formulations are encompassed by the trade name RITUXAN®. Office Action, pages 5-6, item 9. This rejection is respectfully traversed.

As noted above, the RITUXAN® (rituximab) antibody refers to a particular anti-CD20 antibody, which is disclosed in U.S. Patent No. 5,736,137, which issued on April 7, 1998, and therein described using the laboratory designation C2B8. *See* page 25, lines 21-22. Cells expressing the RITUXAN® (rituximab) antibody are publicly available from the American Tissue Type Collection as deposit number 69119. "RITUXAN® (rituximab)" is recognized in the art, including in the claims of issued U.S. Patent Nos. 6,486,204, 6,462,041, and 6,462,017. These claims are presumptively enabled in accordance with 35 U.S.C. § 282. Thus, the examiner's rejection of the present claims as allegedly failing to enable one skilled in the art to practice the invention is inconsistent with the recent issuance of U.S. Patent Nos. 6,486,204, 6,462,041, and 6,462,017. Applicant further submits that the present invention is not limited by any particular formulation, including the variations disclosed in the application as originally filed, for example at page 50, line 20, through page 52, line 19.

Based on the foregoing, applicant believes that a skilled artisan could readily prepare a RITUXAN® (rituximab) composition to use in accordance with the claimed methods. Thus, applicant respectfully requests that this rejection of claims 81-82, 84, 86, and 90 under 35 U.S.C. § 112, first paragraph, also be withdrawn.

Rejection of Claims Under 35 U.S.C. § 103(a)
Based on Alas in view of Levy and Goldenberg

Claims 74-79, 81-87, and 89-96 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Alas et al. (1998) *Blood* 92:601A (Alas) in view of Levy et al. (1994) *J Clin Invest* 93:424-428 (Levy) and U.S. Patent No. 6,183,744 (Goldenberg). In the view of the examiner, it would have been obvious to combine an anti-CD20 antibody with an anti-IL10 antibody because removal of IL10 abolishes the protective effects of bcl-2. The examiner also contends that it would be obvious to further include a chemotherapeutic agent because combination therapy has been shown to treat cancers effectively. Office Action, pages 5-9, item 10. This rejection is respectfully traversed based on the arguments set forth below.

Alas teaches that the C2B8 antibody can be used to sensitize B cell lymphoma cells to cytotoxic agents. Alas observed that cells treated with C2B8 downregulate the expression of IL10. Based thereon, Alas postulated that the C2B8 antibody is effective based on regulation of IL10, which in turn regulates cellular apoptotic proteins. In contrast to the assertion of the examiner, these results do not suggest combination of C2B8 and IL10 as an effective therapy

having anti-cancer efficacy greater than that of either therapy alone. Rather, the studies by Alas suggest that the effects of C2B8 are mediated by resultant changes in 1L10. Based on these results, treatment with an IL10 antagonist would be expected to be redundant to treatment with C2B8, which *teaches away* from the proposed combination. Specifically, the use of C2B8 in conjunction with an IL10 antagonist would be expected to have no greater therapeutic benefit than the use of C2B8 alone. As disclosed in the instant application, the proposed combination yielded unexpected synergistic results (see e.g., page 10, lines 5-8, page 13, lines 1-8).

The deficiency of Alas is not cured by the disclosure of Levy. Levy teaches that IL10 enhances cell viability by inducing bcl-2 expression. This protective effect is abolished on addition of an anti-IL10 antibody. No data is presented or suggested regarding the biological effect of anti-IL10 on cells in the absence of exogenous IL10. Rather, the use of an anti-IL10 antibody in Levy demonstrates only the specificity of IL10-induced cell protection.

The deficiency of Alas is also not cured by the disclosure of Goldenberg. Goldenberg describes treatment of B cell malignancies using an anti-CD22 antibody in combination with chemotherapeutics. The examiner relies on Goldenberg as teaching multimodal therapy, including administration of an anti-CD22 antibody in combination with cytokines, such as IL10 (claim 15). In contrast to Goldenberg, the present invention teaches combination therapies that include the use of IL10 antagonists.

As described above, applicant submits that the combination of a B cell depleting antibody and an IL10 antagonist is not motivated by, and is in fact discouraged by, the teaching of Alas. The mere existence of an IL10 antagonist (*e.g.*, anti-IL10 antibody), as described by Levy, does not suggest or motivate an unobvious use of that antibody. In addition, the existence of combination therapies, for example as described by Goldenberg, does not render obvious combinations contrary to those described or suggested. Thus, the teachings of Alas, Levy, and Goldberg, when considered alone or in combination, fail to motivate the use of an anti-CD20 antibody in combination with IL10 antagonists as recited in the instant claims. Indeed, the teachings of Alas and Goldberg teach away from the present invention.

Applicant further submits that, at the time of the instant invention, the use of IL10 antagonists in cancer therapy was controversial. The literature contained reports that both supported and discounted a correlation between cytokines and disease progression. For

instance, Bonnefoix et al. (1997) *Leuk Lymphoma* 25:169-178 (Bonnefoix) found that cytokines (IL2, IL3, IL4, IL6, IL10, IL13, G-CSF, GM-CSF, interferon alpha and interferon gamma) could either inhibit or stimulate proliferation of lymphoma cells of various histological subtypes. In addition, similar to the methods of Goldenberg, U.S. Patent No. 5,770,190 suggests administration of IL10 (*not* IL10 antagonists as presently claimed) in conjunction with chemotherapeutic agents for treatment of acute leukemia.

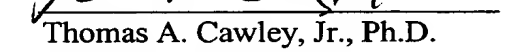
Based on the foregoing arguments, applicant believes that claims 74, 76-79, and 83 are unobvious over the cited references in accordance with 35 U.S.C. § 103(a). Claims 75, 81-82, 84-87, and 89-96 ultimately depend from claims 74, 76-79, and 83 and are therefore also believed to be patentably over the cited references. Thus, applicant respectfully requests that the rejection of claims 74-79, 81-87, and 89-96 under § 103(a) be withdrawn.

Conclusion

All objections and rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP LLP



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